

Exhibit F

Apoptosis

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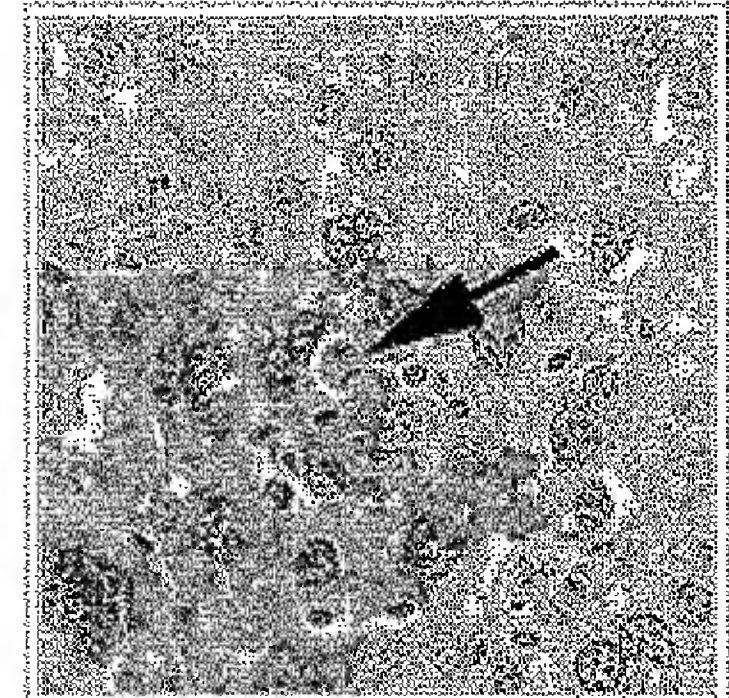
Apoptosis (pronounced /ˌæpəˈtoʊsɪs/^[1]) is the process of programmed cell death (PCD) that may occur in multicellular organisms. Programmed cell death involves a series of biochemical events leading to a characteristic cell morphology and death, in more specific terms, a series of biochemical events that lead to a variety of morphological changes, including blebbing, changes to the cell membrane such as loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation (1-4). (See also Apoptosis DNA fragmentation.) Processes of disposal of cellular debris whose results do not damage the organism differentiate apoptosis from necrosis.

In contrast to necrosis, which is a form of traumatic cell death that results from acute cellular injury, apoptosis, in general, confers advantages during an organism's life cycle. For example, the differentiation of fingers and toes in a developing human embryo occurs because cells between the fingers apoptose; the result is that the digits are separate. Between 50 billion and 70 billion cells die each day due to apoptosis in the average human adult. For an average child between the ages of 8 and 14, approximately 20 billion to 30 billion cells die a day. In a year, this amounts to the proliferation and subsequent destruction of a mass of cells equal to an individual's body weight.

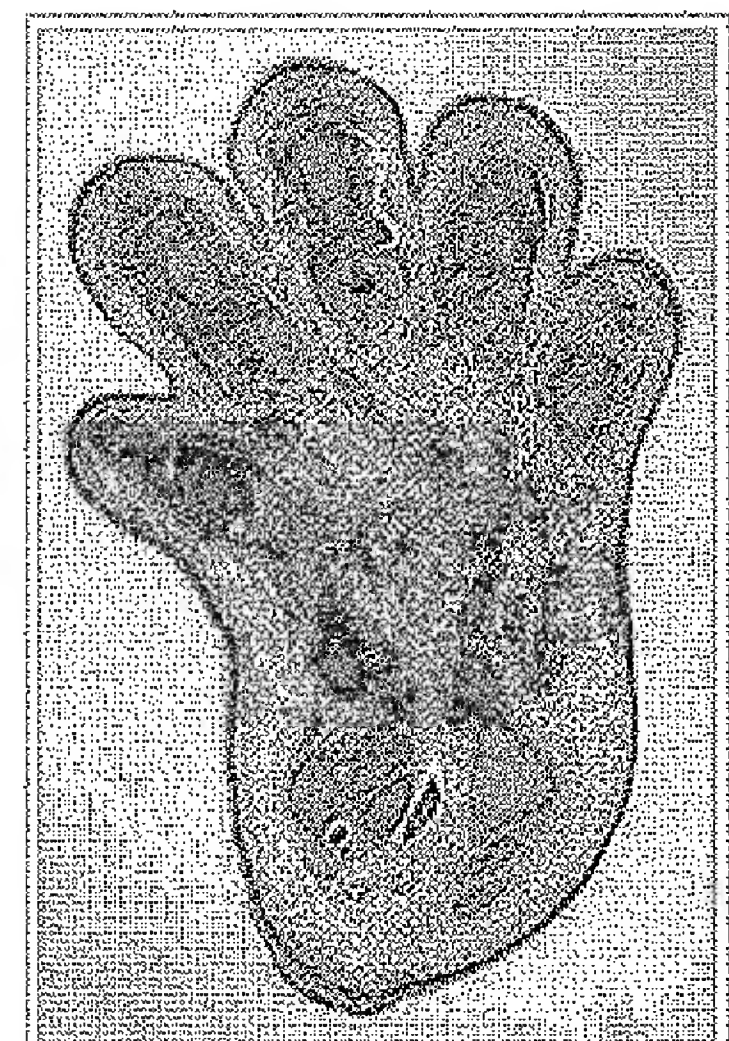
Research on apoptosis has increased substantially since the early 1990s. In addition to its importance as a biological phenomenon, defective apoptotic processes have been implicated in an extensive variety of diseases. Excessive apoptosis causes hypotrophy, such as in ischemic damage, whereas an insufficient amount results in uncontrolled cell proliferation, such as cancer.

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A section of mouse liver showing an apoptotic cell indicated by an arrow



Histologic cross section of embryonic foot of mouse (*Mus musculus*) in 15.5 day of its development. There are still cells between fingers. (Full development of mouse lasts 27 days.) (Compare this image with image of leg of mouse.)

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Discovery and etymology

Cell death is a completely normal process in living organisms and was first discovered by scientists over 100 years ago. A German scientist Carl Vogt was first to describe the principle of apoptosis in 1842. In 1885, anatomist Walther Flemming delivered a more precise description of the process of programmed cell death. However, it was not until 1965 that the topic was resurrected. While studying tissues using electron microscopy, John Foxton Ross Kerr at University of Queensland was able to distinguish apoptosis (Greek: *apo* - from, *ptosis* - falling) from traumatic cell death.^[2] Following the publication of a paper describing the phenomenon, Kerr was invited to join Alastair R Currie, as well as Andrew Wyllie, who was Currie's graduate student,^[3] at University of Aberdeen. In 1972, the trio published a seminal article in the British Journal of Cancer.^[4] Kerr had initially used the term programmed cell necrosis, but in the article, the process of natural cell death was called *apoptosis*. Kerr, Wyllie and Currie credited James Cormack, a professor of Greek language at University of Aberdeen, with suggesting the term apoptosis. Kerr received the Paul Ehrlich and Ludwig Darmstaedter Prize on March 14, 2000, for his description of apoptosis. He shared the prize with Boston biologist Robert Horvitz.^[5]

In Greek, apoptosis translates to "dropping off" of petals or leaves from plants or trees. Cormack reintroduced the term for medical use as it had a medical meaning for the Greeks over two thousand years before. Hippocrates used the term to mean "the falling off of the bones". Galen extended its meaning to "the dropping of the scabs". Cormack was no doubt aware of this usage when he suggested the name. Debate continues over the correct pronunciation, with opinion divided between a pronunciation with a silent *p* (pronounced /æpə'toʊsɪs/) and the *p* pronounced (pronounced /æpəp'toʊsɪs/),^{[1][6]} as in the original Greek. In English, the *p* of the Greek *-pt-* consonant cluster is typically silent at the beginning of a word (e.g. pterodactyl), but articulated when used in combining forms preceded by a vowel, as in helicopter or the orders of insects: diptera, lepidoptera, etc.

It should be noted that in the original Kerr Wyllie and Currie paper, British Journal of Cancer, 1972 Aug;26(4):239-57, there is a footnote regarding the pronunciation.

"We are most grateful to Professor James Cormack of the Department of Greek, University of Aberdeen, for suggesting this term. The word "apoptosis" (Greek spelling of apoptosis) is used in Greek to describe the "dropping off" or "falling off" of petals from flowers, or leaves from trees. To show the derivation clearly, we propose that the stress should be on the penultimate syllable, the second half of the word being pronounced like "ptosis" (with the "p" silent), which comes from the same root "to fall", and is already used to describe the drooping of the upper eyelid."

Functions

Cell termination

Apoptosis occurs when a cell is damaged beyond repair, infected with a virus, or undergoing stressful conditions such as starvation. Damage to DNA from ionizing radiation or toxic chemicals can also induce apoptosis via the actions of the tumour-suppressing gene *p53*. The "decision" for apoptosis can come from the cell itself, from the surrounding tissue, or from a cell that is part of the immune system. In these cases apoptosis functions to remove the damaged cell, preventing it from sapping further nutrients from the organism, or halting further spread of viral infection.

Apoptosis also plays a role in preventing cancer. If a cell is unable to undergo apoptosis because of mutation or biochemical inhibition, it continues to divide and develop into a tumour. For example, infection by papillomaviruses causes a viral gene to interfere with the cell's *p53* protein, an important member of the apoptotic pathway. This interference in the apoptotic capability of the cell plays a role in the development of cervical cancer.

Homeostasis

In the adult organism, the number of cells is kept relatively constant through cell death and division. Cells must be replaced when they malfunction or become diseased, but proliferation must be offset by cell death.^[7] This control mechanism is part of the homeostasis required by living organisms to maintain their internal states within certain limits. Some scientists have suggested homeodynamics as a more accurate term.^[8] The related term *allostasis* reflects a balance of a more complex nature by the body.

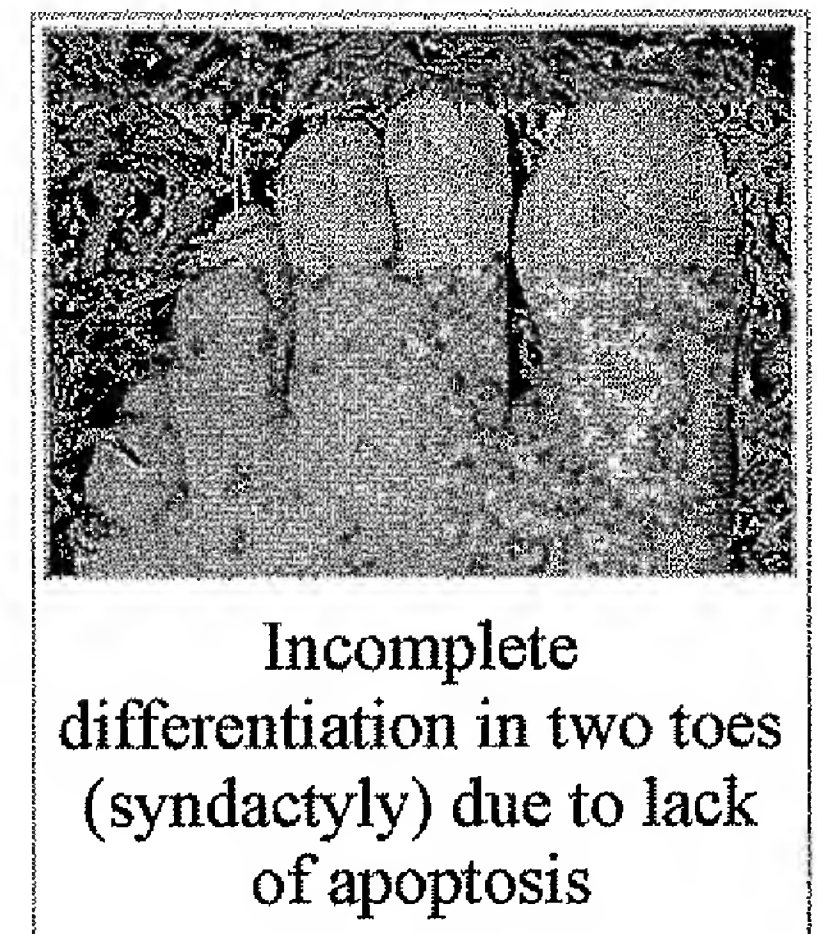
Homeostasis is achieved when the rate of mitosis (cell division) in the tissue is balanced by cell death. If this equilibrium is disturbed, one of two potentially fatal disorders occurs:

- the cells are dividing faster than they die, effectively developing a tumor.
- the cells are dividing slower than they die, causing cell loss.

Homeostasis involves a complex series of reactions, a ongoing process inside an organism that calls for different types of cell signaling. Any impairment can cause a disease. For example, dysregulation of signaling pathway has been implicated in several forms of cancer. The pathway, which conveys an anti-apoptotic signal, has been found to be activated in pancreatic adenocarcinoma tissues.

Development

Programmed cell death is an integral part of both plant and animal tissue development. Development of an organ or tissue is often preceded by the extensive division and differentiation of a particular cell, the resultant mass is then "pruned" into the correct form by apoptosis. Unlike necrosis, cellular death caused by injury, apoptosis results in cell shrinkage and fragmentation. Such shrinkage and fragmentation allow the cells to be phagocytosed and their components reused without releasing potentially harmful intracellular substances such as hydrolytic enzymes into the surrounding tissue.



Research on chick embryos has suggested how selective cell proliferation, combined with selective apoptosis, sculpts developing tissues in vertebrates. During vertebrate embryo development, structures called the notochord and the floor plate secrete a gradient of the signaling molecule (Shh), and it is this gradient that directs cells to form patterns in the embryonic neural tube. Cells that receive Shh in a receptor in their membranes called patched1 (Ptc1) survive and proliferate. In the absence of Shh, one of

the ends of this same Ptc1 receptor (the carboxyl-terminal, inside the membrane) is cleaved by caspase-3, an action that exposes an apoptosis-producing domain.^{[9][10]}

During development, apoptosis is tightly regulated and different tissues use different signals for inducing apoptosis. In birds, bone morphogenetic proteins (BMP) signaling is used to induce apoptosis in the interdigital tissue. In *Drosophila* flies, steroid hormones regulate cell death. Developmental cues can also induce apoptosis, such as the sex-specific cell death of hermaphrodite specific neurons in *C. elegans* males through low *TRA-1* transcription factor activity (*TRA-1* helps prevent cell death).

Lymphocyte interactions

The development of B lymphocytes and T lymphocytes in a human body is a complex process that creates a large pool of diverse cells and subsequently eliminates those potentially damaging to the body. Apoptosis is the mechanism by which the body removes both the ineffective and the potentially damaging immature cells. In T cells, apoptosis is initiated by the withdrawal of survival signals.^[11]

Cytotoxic T cells are able to directly induce apoptosis by opening up pores in the target's membrane and releasing chemicals that bypass the normal apoptotic pathway. The pores are created by the action of secreted perforin, and the granules contain granzyme B, a serine protease that activates a variety of caspases by cleaving aspartate residues.^[12]

Process

The process of apoptosis is controlled by a diverse range of cell signals, which may originate either extracellularly (*extrinsic inducers*) or intracellularly (*intrinsic inducers*). Extracellular signals may include toxins^[13], hormones, growth factors, nitric oxide^[14] or cytokines, and therefore must either cross the plasma membrane or transduce to effect a response. These signals may positively or negatively induce apoptosis. The binding and subsequent initiation of apoptosis by a molecule is termed positive, whereas the active repression of apoptosis by a molecule is termed negative.

A cell initiates intracellular apoptotic signalling in response to a stress, which may bring about cell suicide. The binding of nuclear receptors by glucocorticoids^[12], heat^[12], radiation^[12], nutrient deprivation^[12], viral infection^[12], hypoxia^[12] and increased intracellular calcium concentration^[15], for example, by damage to the membrane can all trigger the release of intracellular apoptotic signals by a damaged cell. A number of cellular components, such as poly ADP ribose polymerase, may also help regulate

apoptosis.^[16]

Before the actual process of cell death is carried out by enzymes, apoptotic signals must cause regulatory proteins to start off the death pathway. This step allows apoptotic signals to cause cell death, or the process to be stopped, should the cell no longer need to die. Several proteins are involved, but two main methods of regulation have been identified: targeting mitochondria functionality, or directly transducing the signal via *adapter proteins* to the apoptotic mechanisms.

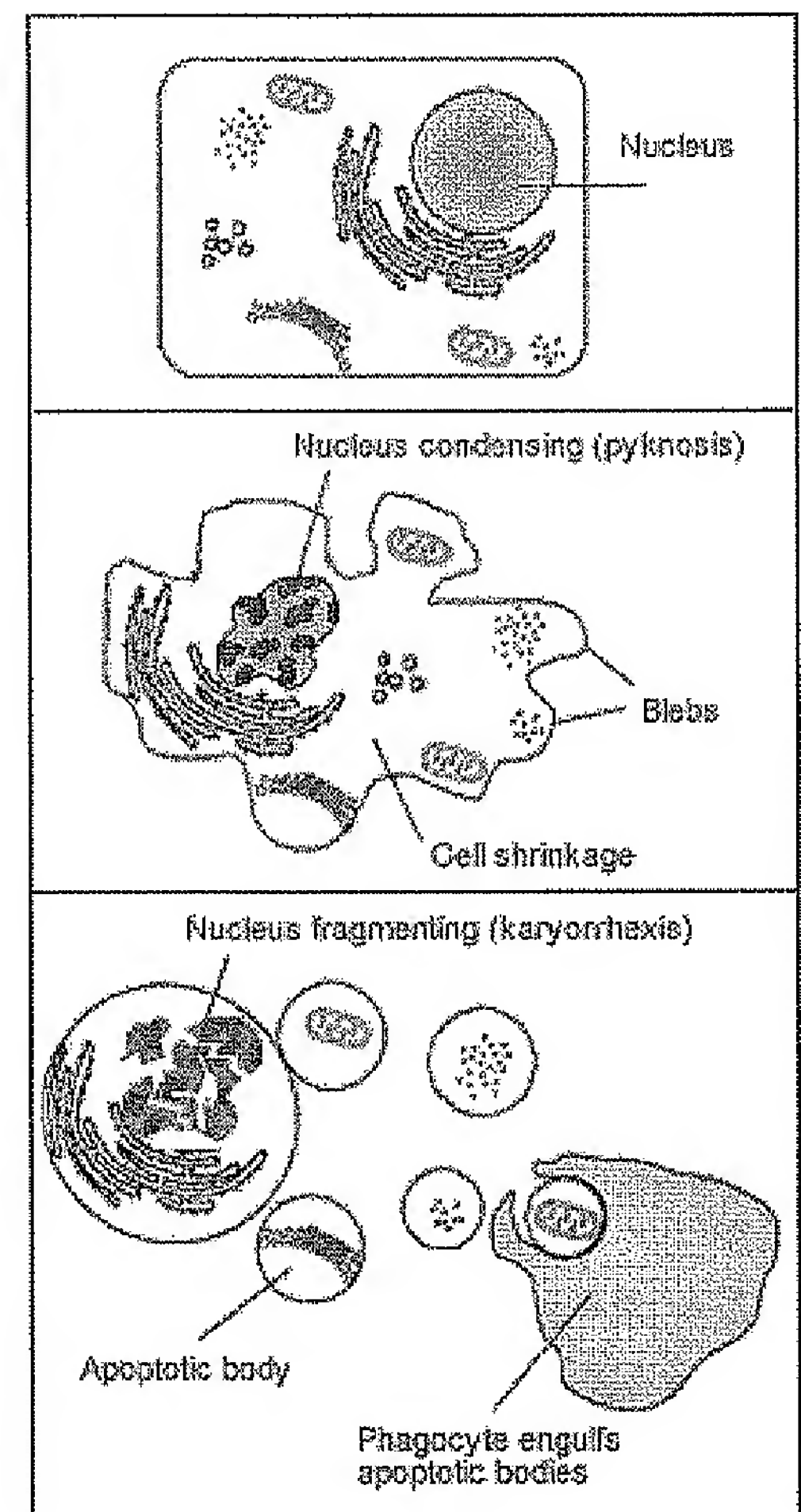
Mitochondrial regulation

The mitochondria are essential to multicellular life. Without them, a cell ceases to respire aerobically and quickly dies, a fact exploited by some apoptotic pathways. Apoptotic proteins that target mitochondria affect them in different ways. They may cause mitochondrial swelling through the formation of membrane pores, or they may increase the permeability of the mitochondrial membrane and cause apoptotic

effectors to leak out.^[12] There is also a growing body of evidence that indicates that nitric oxide is able to induce apoptosis by helping to dissipate the membrane potential of mitochondria and therefore make it more permeable.^[14]

Mitochondrial proteins known as SMACs (second mitochondria-derived activator of caspases) are released into the cytosol following an increase in permeability. SMAC binds to *inhibitor of apoptosis proteins* (IAPs) and deactivates them, preventing the IAPs from arresting the apoptotic process and therefore allowing apoptosis to proceed. IAP also normally suppresses the activity of a group of cysteine proteases called caspases,^[17] which carry out the degradation of the cell, therefore the actual degradation enzymes can be seen to be indirectly regulated by mitochondrial permeability.

Cytochrome c is also released from mitochondria due to formation of a channel, MAC, in the outer mitochondrial membrane^[18], and serves a regulatory function as it precedes morphological change associated with apoptosis.^[12] Once cytochrome c is released it binds with *Apaf-1* and ATP, which then bind to *pro-caspase-9* to create a protein complex known as an apoptosome. The apoptosome cleaves the pro-caspase to its active form of



caspase-9, which in turn activates the effector *caspase-3*.

MAC is itself subject to regulation by various proteins, such as those encoded by the mammalian *Bcl-2* family of anti-apoptotic genes, the homologs of the *ced-9* gene found in *C. elegans*.^{[19][20]} *Bcl-2* proteins are able to promote or inhibit apoptosis either by direct action on MAC or indirectly through other proteins. It is important to note that the actions of some *Bcl-2* proteins are able to halt apoptosis even if cytochrome c has been released by the mitochondria.^[12]

Direct signal transduction

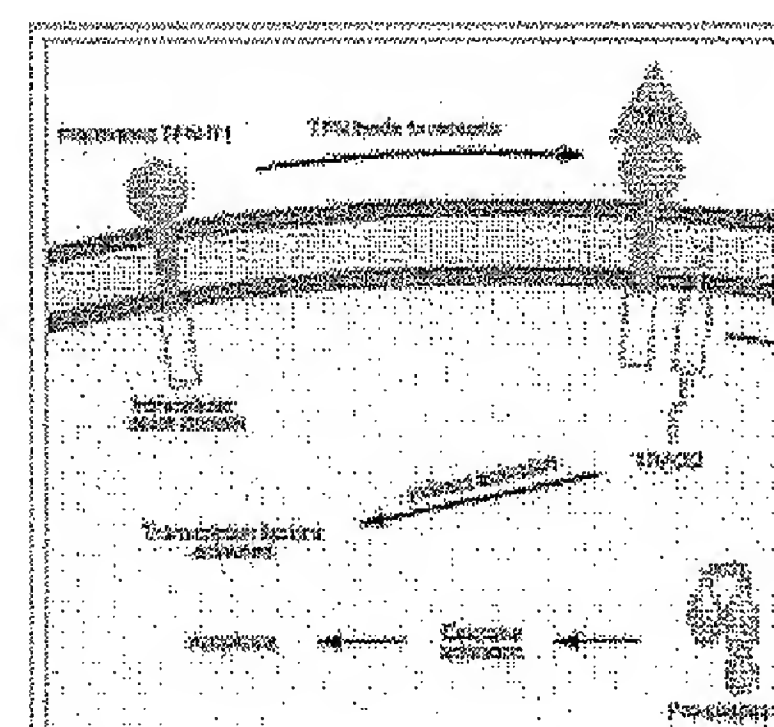
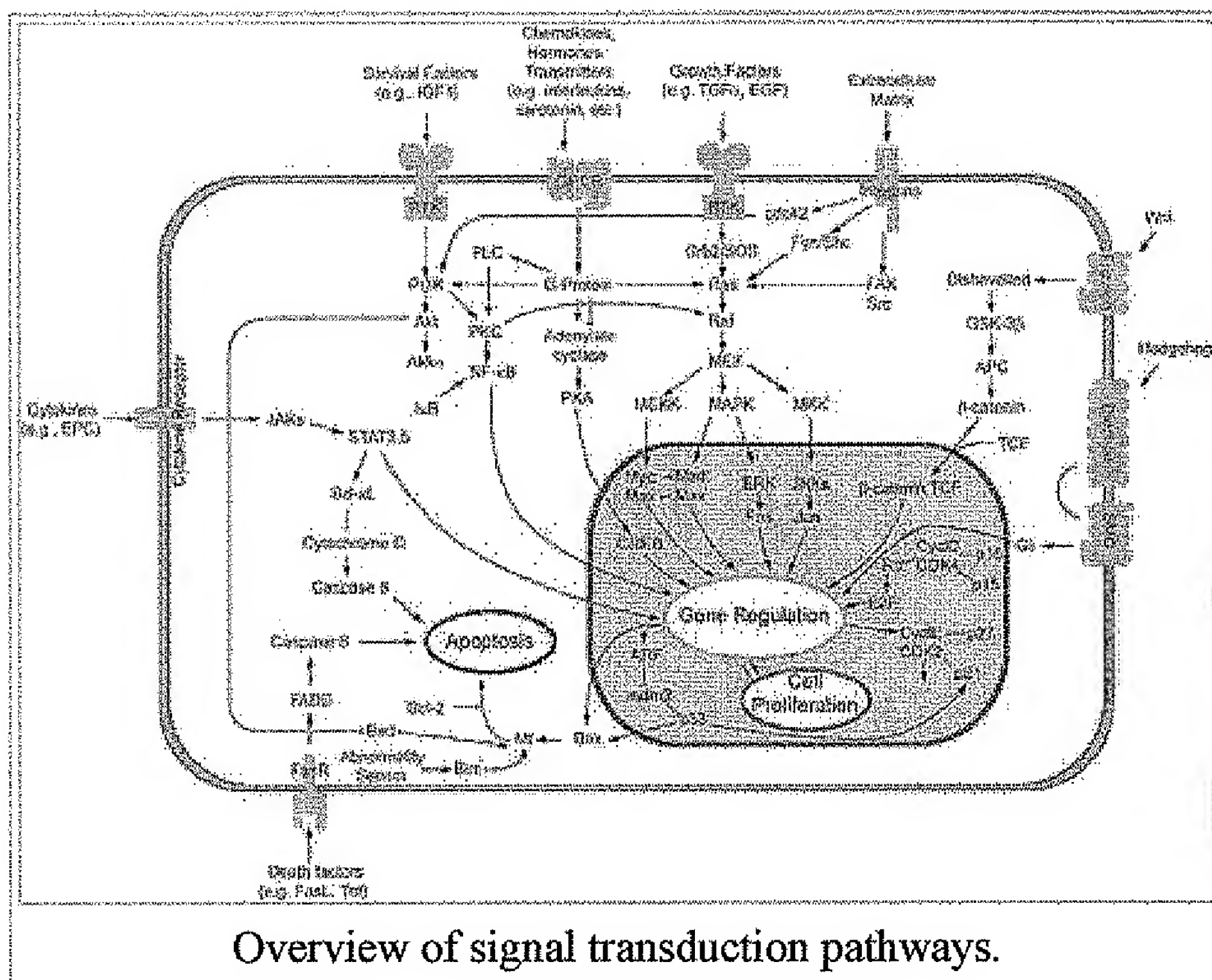
Two theories of the direct initiation of apoptotic mechanisms in mammals have been suggested: the *TNF-induced* (tumour necrosis factor) model and the *Fas-Fas ligand-mediated* model, both involving receptors of the *TNF receptor* (TNFR) family^[21] coupled to extrinsic signals.

TNF is a cytokine produced mainly by activated macrophages, and is the major extrinsic mediator of apoptosis.

Most cells in the human

body have two receptors for TNF: *TNF-R1* and *TNF-R2*. The binding of TNF to *TNF-R1* has been shown to initiate the pathway that leads to caspase activation via the intermediate membrane proteins *TNF receptor-associated death domain* (TRADD) and *Fas-associated death domain protein* (FADD).

^[22] Binding of this receptor can also indirectly lead to the activation of transcription factors involved in cell survival and inflammatory responses.^[23] The link between TNF and apoptosis shows why an abnormal production of TNF plays a fundamental role in several human diseases, especially in



autoimmune diseases.

signal transduction

The Fas receptor (also known as *Apo-1* or *CD95*) binds the Fas ligand (FasL), a transmembrane protein part of the TNF family.^[21] The interaction between Fas and FasL results in the formation of the *death-inducing signaling complex* (DISC), which contains the FADD, caspase-8 and caspase-10. In some types of cells (type I), processed caspase-8 directly activates other members of the caspase family, and triggers the execution of apoptosis. In other types of cells (type II), the *Fas*-DISC starts a feedback loop that spirals into increasing release of pro-apoptotic factors from mitochondria and the amplified activation of caspase-8.^[24]

Following *TNF-R1* and *Fas* activation in mammalian cells a balance between pro-apoptotic (BAX,^[25] BID, BAK, or BAD) and anti-apoptotic (*Bcl-Xl* and *Bcl-2*) members of the *Bcl-2* family is established. This balance is the proportion of pro-apoptotic homodimers that form in the outer-membrane of the mitochondrion. The pro-apoptotic homodimers are required to make the mitochondrial membrane permeable for the release of caspase activators such as cytochrome c and SMAC. Control of pro-apoptotic proteins under normal cell conditions of non-apoptotic cells is incompletely understood, but it has been found that a mitochondrial outer-membrane protein, VDAC2, interacts with BAK to keep this potentially-lethal apoptotic effector under control.^[26] When the death signal is received, products of the activation cascade displace VDAC2 and BAK is able to be activated.

There also exists a caspase-independent apoptotic pathway that is mediated by AIF (apoptosis-inducing factor).^[27]

Execution

Many pathways and signals lead to apoptosis, but there is only one mechanism that actually causes the death of a cell. After a cell receives stimulus, it undergoes organized degradation of cellular organelles by activated proteolytic caspases. A cell undergoing apoptosis shows a characteristic morphology:

1. Cell shrinkage and rounding are shown because of the breakdown of the proteinaceous cytoskeleton by caspases.
2. The cytoplasm appears dense, and the organelles appear tightly packed.
3. Chromatin undergoes condensation into compact patches against the nuclear envelope in a process known as pyknosis, a hallmark of apoptosis.^{[28][29]}
4. The nuclear envelope becomes discontinuous and the DNA inside it is fragmented in

a process referred to as karyorrhexis. The nucleus breaks into several discrete *chromatin bodies* or *nucleosomal units* due to the degradation of DNA.^[30]

5. The cell membrane shows irregular buds known as blebs.

6. The cell breaks apart into several vesicles called *apoptotic bodies*, which are then phagocytosed.

Apoptosis progresses quickly and its products are quickly removed, making it difficult to detect or visualize. During karyorrhexis, endonuclease activation leaves short DNA fragments, regularly spaced in size. These give a characteristic "laddered" appearance on agar gel after electrophoresis. Tests for DNA laddering differentiate apoptosis from ischemic or toxic cell death.^[31]

Removal of dead cells

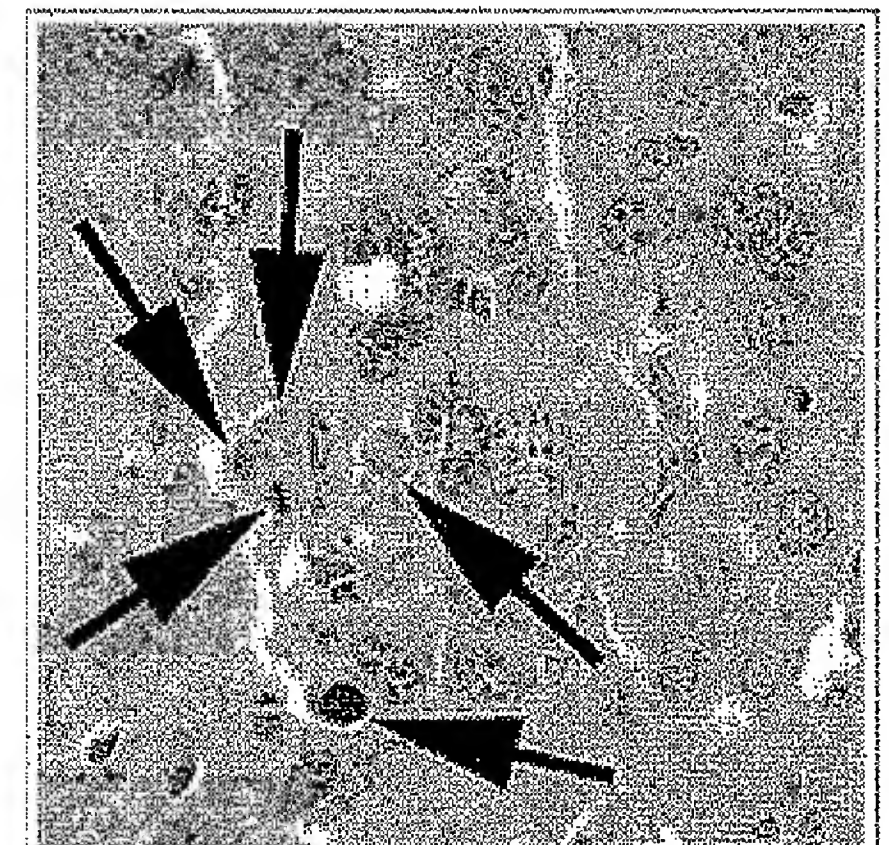
The removal of dead cells by neighboring phagocytic cells has been termed efferocytosis.

^[32] Dying cells that undergo the final stages of apoptosis display phagocytotic molecules, such as phosphatidylserine, on their cell surface.^[33] Phosphatidylserine is normally found on the cytosolic surface of the plasma membrane, but is redistributed during apoptosis to the extracellular surface by a hypothetical protein known as scramblase.^[34] These molecules mark the cell for phagocytosis by cells possessing the appropriate receptors, such as macrophages.^[35] Upon recognition, the phagocyte reorganizes its cytoskeleton for engulfment of the cell. The removal of dying cells by phagocytes occurs in an orderly manner without eliciting an inflammatory response.

Implication in disease

Defective apoptotic pathways

The many different types of apoptotic pathways contain a multitude of different biochemical components, many of them not yet understood.^[7] As a pathway is more or less sequential in nature, it is a victim of causality; removing or modifying one component leads to an effect in another. In a living organism this can have disastrous effects, often in the form of disease or disorder. A discussion of every disease caused by modification of the various apoptotic pathways would be impractical, but the concept overlying each one is the same: the normal functioning of the pathway has been



A section of mouse liver showing several apoptotic cells, indicated by arrows

disrupted in such a way as to impair the ability of the cell to undergo normal apoptosis. This results in a cell that lives past its "use-by-date" and is able to replicate and pass on any faulty machinery to its progeny, increasing the likelihood of the cell becoming cancerous or diseased.

A recently-described example of this concept in action can be seen in the development of a lung cancer called NCI-H460.^[36] The *X-linked inhibitor of apoptosis protein* (XIAP) is overexpressed in cells of the H460 cell line. XIAPs bind to the processed form of caspase-9, and suppress the activity of apoptotic activator cytochrome c, therefore overexpression leads to a decrease in the amount of pro-apoptotic agonists. As a consequence, the balance of anti-apoptotic and pro-apoptotic effectors is upset in favour of the former, and the damaged cells continue to replicate despite being directed to die.

Dysregulation of p53

The tumor-suppressor protein p53 accumulates when DNA is damaged due to a chain of biochemical reactions. Part of this pathway includes alpha-interferon and beta-interferon, which induce transcription of the *p53* gene and result in the increase of p53 protein level and enhancement of cancer cell-apoptosis.^[37] p53 prevents the cell from replicating by stopping the cell cycle at G1, or interphase, to give the cell time to repair, however it will induce apoptosis if damage is extensive and repair efforts fail. Any disruption to the regulation of the *p53* or interferon genes will result in impaired apoptosis and the possible formation of tumors.

HIV progression

The progression of the human immunodeficiency virus infection to AIDS is primarily due to the depletion of CD4+ T-helper lymphocytes, which leads to a compromised immune system. One of the mechanisms by which T-helper cells are depleted is apoptosis, which results from a series of biochemical pathways:^[38]

1. HIV enzymes deactivate anti-apoptotic *Bcl-2* This does not directly cause cell death, but primes the cell for apoptosis should the appropriate signal be received. In parallel these enzymes activate pro-apoptotic *procaspase-8*, which does directly activate the mitochondrial events of apoptosis.
2. HIV may increase the level of cellular proteins which prompt Fas-mediated apoptosis.
3. HIV proteins decrease the amount of CD4 glycoprotein marker present on the cell membrane.
4. Released viral particles and proteins present in extracellular fluid are able to induce apoptosis in nearby "bystander" T helper cells.
5. HIV decreases the production of molecules involved in marking the cell for

apoptosis, giving the virus time to replicate and continue releasing apoptotic agents and virions into the surrounding tissue.

6. The infected CD4⁺ cell may also receive the death signal from a cytotoxic T cell.

Cells may also die as a direct consequence of viral infection.

Viral infection

Viruses can trigger apoptosis of infected cells via a range of mechanisms including:

- Receptor binding.
- Activation of protein kinase R (PKR).
- Interaction with p53.
- Expression of viral proteins coupled to MHC proteins on the surface of the infected cell, allowing recognition by cells of the immune system (such as Natural Killer and cytotoxic T cells) that then induce the infected cell to undergo apoptosis.^[39]

Most viruses encode proteins that can inhibit apoptosis.^[40] Several viruses encode viral homologs of Bcl-2. These homologs can inhibit pro-apoptotic proteins such as BAX and BAK, which are essential for the activation of apoptosis. Examples of viral Bcl-2 proteins include the Epstein-Barr virus BHRF1 protein and the adenovirus E1B 19K protein.^[41] Some viruses express caspase inhibitors that inhibit caspase activity and an example is the CrmA protein of cowpox viruses. Whilst a number of viruses can block the effects of TNF and Fas. For example the M-T2 protein of myxoma viruses can bind TNF preventing it from binding the TNF receptor and inducing a response.^[42] Furthermore, many viruses express p53 inhibitors that can bind p53 and inhibit its transcriptional transactivation activity. Consequently p53 cannot induce apoptosis since it cannot induce the expression of pro-apoptotic proteins. The adenovirus E1B-55K protein and the hepatitis B virus HBx protein are examples of viral proteins that can perform such a function.^[43]

Interestingly, viruses can remain intact from apoptosis particularly in the latter stages of infection. They can be exported in the *apoptotic bodies* that pinch off from the surface of the dying cell and the fact that they are engulfed by phagocytes prevents the initiation of a host response. This favours the spread of the virus.^[42]

Apoptosis in plants

Programmed cell death in plants has a number of molecular similarities to animal apoptosis, but it also has differences, notably the presence of a cell wall and the lack of an

immune system which removes the pieces of the dead cell. Instead of an immune response, the dying cell synthesizes substances to break itself down and places them in a vacuole which ruptures as the cell dies. Whether this whole process resembles animal apoptosis closely enough to warrant using the name *apoptosis* (as opposed to the more general *programmed cell death*) is unclear.^[44]

Caspase Independent Apoptosis

There is an extrinsic pathway that has been noticed in several toxical studies that have shown that an increase in calcium concentration within a cell caused by drug activity; also has the ability to cause apoptosis via a calcium binding protease calpain.

- Anoikis
- Apaf-1
- Apo2.7
- Apoptosis DNA Fragmentation
- Autolysis
- Autophagy
- Autophagy network
- Cisplatin
- Entosis
- Immunology
- Necrosis

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- Apoptosis & Caspase 3, The Proteolysis Map-animation
- Apoptosis & Caspase 8, The Proteolysis Map-animation
- Apoptosis & Caspase 7, The Proteolysis Map-animation
- Apoptosis (Programmed Cell Death) - The Virtual Library of Biochemistry and Cell Biology
- Apoptosis Research Portal
- Apoptosis Info Apoptosis protocols, articles, news, and recent publications.
- Database of proteins involved in apoptosis
- Apoptosis Video
- The Mechanisms of Apoptosis Kimball's Biology Pages. Simple explanation of the mechanisms of apoptosis triggered by internal signals (bcl-2), along the caspase-9, caspase-3 and caspase-7 pathway; and by external signals (FAS and TNF), along the caspase 8 pathway. Accessed 25 March 2007.
- WikiPathways - Apoptosis pathway
- Finding Cancer's Self-Destruct Button CR magazine (Spring 2007). Article on apoptosis and cancer.
- Apoptosis on-line lecture by Wang Xiaodong

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